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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/503,596	02/11/2000	Mu-en Lee	05433-042001	6895

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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	15

DATE MAILED: 08/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/503,596	Applicant(s) LEE ET AL.	
	Examiner Mary Schmidt	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-23 is/are pending in the application.

4a) Of the above claim(s) 13-23 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 11 February 2000 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election without traverse of claims 1-12 in Paper No. 11 is acknowledged.

2. Claims 13-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons of record as set forth in the Official Action mailed 11/23/01.

Applicant's arguments filed 3/23/02 have been fully considered but they are not persuasive.

The claims as amended are drawn to a methods of inhibiting formation of an atherosclerotic lesion in a mammal or inhibiting differentiation of a macrophage into a foam cell via administration to any species of mammal any compound which reduces expression of

AFABP, specifically the sequences of SEQ ID NO:4 and 8. The specification as filed teaches in Example 1 a knock-out of the AFABP in mice and the correlation between AFABP expression and atherosclerosis.

Applicant states on page 4 of the response that "[t]he design and structure of AFABP inhibitors is taught by the specification and is now defined by the amended claims."

However, the amendment of the claims to specify the AFABP target proteins, does not further describe a representative number of species of the inhibitors to said sequences. **MPEP 2163** teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> **The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying**

characteristics, sufficient to show the applicant was in possession of the claimed genus.

As argued previously, the claims are not adequately described for a representative number of inhibitors to the claimed AFABP sequences for the functions claimed. The MPEP specifically states that the invention as a whole is not adequately described by a functional characteristic. In the instant case, there is no art-recognized correlation or relationship known between any AFABP inhibitor and the claimed functions in vivo. See the 35 U.S.C. 112, first paragraph, lack of enablement rejection below for new references cited to support the assertions made in the previous Official Action of a high level of unpredictability in the art for design and administration of an inhibitor such as antisense to a claimed target sequence *in vivo* as presently claimed. The art at the time the invention was made did not teach specific design criteria or characteristics of a representative number of species of inhibitors to the claimed AFABP molecules with a clear correlation or nexus to the claimed functions. Without such as teaching, one skilled in the art would not have recognized that Applicant was in possession of a representative number of species of such inhibitors from the teachings of the specification as filed. As argued previously, generation of a knock-out mouse does not provide guidance for making inhibitors to the knocked-out target gene since design of inhibitors is a separate art and requires entirely different set of considerations for gene therapeutic applications *in vivo*. In the absence of specific guidance for the design characteristics of a representative number of species of the claimed inhibitors, one skilled in the art would not have been able to readily envisage the structure of the inhibitors claimed having specific functions from the teachings of the

specification as filed. As such, the inhibitors claimed for methods of reducing expression of AFABP are not adequately described.

5. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons of record as set forth in the Official Action mailed 11/23/01.

Applicant's arguments filed 3/23/02 have been fully considered but they are not persuasive.

The claims as amended are drawn to a methods of inhibiting formation of an atherosclerotic lesion in a mammal or inhibiting differentiation of a macrophage into a foam cell via administration to any species of mammal any compound which reduces expression of AFABP, specifically the sequences of SEQ ID NO:4 and 8. The specification as filed teaches in Example 1 a knock-out of the AFABP in mice and the correlation between AFABP expression and atherosclerosis.

Applicant states on page 4 of the response that "[t]he two publications upon which the Examiner relied in support of the enablement rejection date from 1998. Applicant submits that the claimed methods would not require undue experimentation because the state of the art of gene therapy has progressed significantly since the Branch and Flanagan articles were written. Specifically, regarding Flanagan, Applicant notes that the difficulties raised by Flanagan, e.g.,

targeting to tumors, are not an issue in the present invention, because the target tissue (blood vessels) and target cells (macrophages) are easily accessible by intravenous administration."

The arguments raised in the previous Official Action on the merits were drawn to design to any type of novel inhibitor to a specific target sequence, including antisense, ribozyme, protein or small molecule inhibitor. However, since the specification as filed substantially refers to design of antisense as an inhibitory compound (see pages 9-11), the lack of enablement rejection considered antisense especially as the desired type of inhibitory compound claimed. However, the other types of inhibitory molecules were also addressed. In response to Applicants assertions above, the following new references have been added to point out that despite an increase in isolated successes in the antisense field for treatment purposes, these successes do not correlate to design and administration of any antisense to any target gene for any treatment purpose, and thus each antisense must be evaluated on an antisense-by-antisense basis. The following references show that at the time the instant invention was filed, the concerns raised by Branch and Flanagan were apparent in the antisense art:

There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage

using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P.

103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetic,

pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecule (page 9 of the instant specification) *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

The factors considered unpredictable for other types of inhibitory compounds were raised in the previous Official Action as well.

Applicant states on page 5 of the response that "[t]he factors to be analyzed in determining whether undue experimentation is required to practice the full scope of the claims are discussed in In re Wands." Each of Applicants points is addressed:

In regards to "the nature of the invention and state of the prior art" Applicant states that "the Examiner's position is that the nature of the art is antisense therapy and that the state of the art is that it is generally unpredictable." As stated above, the specific focus of the rejection pertaining to antisense was based on Applicants' disclosure which provided more emphasis on design of antisense inhibitors than other types of inhibitory compounds. As reiterated above, the state of the prior art for design of functional antisense for administration *in vivo* for the treatment effects claimed was highly unpredictable.

Applicants state that "[a]lthough the use of antisense is encompassed by the claims, the nature of the invention is inhibition of gene expression. Inhibition of gene expression can be accomplished using a variety of methods known in the art, e.g., antisense, ribozymes, organic compounds." The previous Official Action mailed 11/23/01 also generally contemplated the unpredictable factors for design of non-antisense inhibitors (pages 6 and 7). Applicants state that "[t]he state of the art is that once a target gene is identified and its sequence determined, it is well within the skill of one practicing in the art of molecular medicine to reduce the expression of the target gene." However, as newly cited above, several references in the field of antisense therapy teach that it is not well-within the skill of those in the field to design an antisense for therapeutic purposes absent significant "trial and error" experimentation. Although Applicants have "made a significant contribution to the art by identifying a gene that is directly involved in the development of atherosclerosis, a progressive disease that affects millions of individuals", the

specification as filed has not demonstrated how to make and use any inhibitor of the AFABP gene for the functions claimed in a whole organism.

In regards to "predictability or unpredictability in the art" Applicants submit that "the art of antisense may at one time have been considered an "unpredictable" art; however, the state of the art has changed such that antisense therapy is no longer considered unpredictable." Applicants further state that "[a]ntisense technology has been in development for nearly a decade. Successes with antisense therapy to specifically inhibit gene expression and reduce pathological symptoms in animals have been reported for several years." Applicant then cites the progress of ISIS Pharmaceuticals, Inc. to show that "[a] number of antisense compositions targeting a variety of genes are currently in human clinical trials... for the treatment of cancers, diabetes, and inflammatory and infectious diseases. At least one antisense nucleic acid composition has been approved by the Food & Drug Administration (FDA) for human therapy. For example, an antisense compound targeting viral DNA for the treatment of CMV retinitis in humans was approved by the FDA for marketing in the United States in 1998.... Thus, the foundation for making and administering antisense compositions for treatment of disease is well established."

In response, the references cited above establish that the field of antisense therapy was still unpredictable for design of antisense for use in a whole organism at the time the instant invention was made. The factors considered unpredictable argued above must be considered on an antisense-by-antisense basis since the success or failure of one antisense for administration *in*

vivo for one kind of treatment effect does not correlate to the success or failure of other specific antisense for other treatment effects. As argued previously and above, the success of an antisense in cells in culture (or even in rodents) does not provide an expectation of success for that same antisense in a human. The isolated successes demonstrated by ISIS Pharmaceuticals Inc. are the result of drug discovery of specific antisense, specific types of administration, and specific intended uses. It is not predictable that an antisense which inhibits a target gene in cells in culture will function equivalently in a whole organism in view of the numerous unpredictable considerations found in a whole organism as argued above. Thus a high level of unpredictability in the art was still a consideration for the enablement of the instant invention at the time of filing of the instant specification.

In regards to "presence or absence of working examples" Applicant notes that "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or "prophetic." A working example is based on work actually performed, while a prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved." Applicant then discusses the teachings of the instant specification which show mice having a null mutation in the genes for apoE or both apoE and AFABP and states that [a]n in vitro or in vivo animal model example in the specification, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention."

However, as discussed in the previous Official Action and reiterated above, the teachings of the knock-out mouse do not correlate with the design of specific inhibitors to the knocked-out genes. Although the examples in the specification as filed do not need to be "working" examples, the need for an example does arise particularly in a highly unpredictable art where there is not an expectation of success that the claimed methods will function as claimed. This argument was made in regards to antisense inhibition of the AFABP gene *in vivo* for instance since the art taught that it was not predictable for a prophetic design of an antisense to function for treatment purposes in a whole organism. This argument is based on the unpredictability in the antisense art regarding the mechanics of antisense inhibition *in vivo*. Thus it applied generally to design of antisense to any target gene *in vivo*. Although Applicant has provided evidence of a new role of AFABP in a known human disease, such a teaching does not further alleviate the unpredictability in the art for reducing expression of this target gene *in vivo* by a gene inhibitory mechanism such as antisense.

In regards to the "amount of direction or guidance presented" Applicant points to regions of the instant specification (pages 7-9) teaching specific nucleotides to be administered. However, such a teaching is not substantial enough in view of the high level of unpredictability in the art cited above. Furthermore, the guidance provided in the specification as filed in regards to design of other types of inhibitors, or targeting inhibitors to specific cells *in vivo* is not considered substantial enough for the reasons argued previously and above. Just like design of antisense inhibitors for use *in vivo* is an antisense-by-antisense process, so is design of other

inhibitors such as antibodies. Use of an antibody *in vivo* for one type of therapeutic effect does not correlate to design and use of antibodies to reduce expression of AFABP as instantly claimed. Any *in vivo* therapeutic application has factors to be considered (argued previously) that are unique to each therapeutic agent. To teach how to make and use a claimed therapeutic agent, a disclosure must provide an expectation of success for using the embodiment for the claimed functions. In view of the high level of unpredictability in the art for gene therapy, antisense and other types of therapeutic compounds, the instant disclosure has not met this burden of providing a sufficient level of guidance to make and use the claimed invention.

In regards to the "relative skill of those in the prior art" Applicant writes that "[t]he skilled artisan in the relevant field is a molecular biologist or medical doctor." Applicant further writes that "the hurdles that remain in antisense technology (e.g., delivery issues raised by the Examiner) have largely been overcome. For example, success in antisense therapy to treat a vascular disease (hypertension) has been reported in animals and will proceed to clinical trials (Philips...). Applying the same protocols and principles to treating another vascular disease is well within the skill of those in the art. Although optimization will likely require some experimentation, it is not deemed to be undue for those skilled in the art of molecular medicine."

In response, the references newly cited above support a teaching of unpredictability in the art of antisense, for instance, at the time the instant invention was made. They teach that the hurdles have not been overcome and suggest that antisense success *in vivo* must be evaluated on an individual antisense basis. The success of one antisense (such as that taught by Philips et al.)

does not correlate to the success of any antisense to any target gene for the treatment of vascular disease as argued by Applicant. As such, without further guidance as to specific antisense having an expectation of success to function as claimed, one of skill in the art would have had to practice substantial amount of trial and error experimentation, an amount considered undue, to practice the instantly claimed invention.

In regards to the "quantity of experimentation necessary" Applicant states that "all of the techniques required to practice the claimed methods were described in the specification or were known to those skilled in the art as of the filing date." Applicants further state that "[g]iven the correlation between atherosclerosis and expression of AFABP that has been established in an art-recognized animal model for atherosclerosis, and the level of skill in the relevant art, Applicants submit that the undue experimentation would not be required of one skilled in the art to practice the claimed invention."

However, as argued previously, the teachings in the specification as filed for design of inhibitors to AFABP are not considered sufficient to teach one skilled in the art how to design functional inhibitors of AFABP for the specific therapeutic functions claimed. Specifically, the teachings of the specification as filed do not provide guidance as to how to overcome the high level of unpredictability in the art for design of any such functional gene therapeutic compound. Applicant states that "[t]he issues raised by the Examiner fall into the category of routine experimentation, e.g., determination of formulation, dose, and mode of delivery, which is permitted by the statutory requirements for enablement." However, although routine

experimentation is allowed, the factors cited are considered more than routine experimentation since they vary significantly based on the type and structure of therapeutic molecule administered. The argument is upheld that such factors are highly unpredictable and were not generally known for determination of how to make and use any AFABP inhibitor for the claimed functions at the time the invention was made. Since the new references were added to support the teachings of Branch and Flanagan, the state of the prior art for antisense gene therapy is shown to have been unpredictable at the time the instant invention was made. The teachings of Philips et al. do not further provide generic guidance for the design of any functional therapeutic compound for inhibiting formation of atherosclerotic lesions in any mammal via reducing the expression of AFABP.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Kay Pinkney*, whose telephone number is (703) 305-3553.

M. M. Schmidt
August 11, 2002

M Schmidt

Attachment for PTO-948 (Rev. 03/01, or earlier)
6/18/01

The below text replaces the pre-printed text under the heading, "Information on How to Effect Drawing Changes," on the back of the PTO-948 (Rev. 03/01, or earlier) form.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the Notice of Allowability. Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a).

Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.